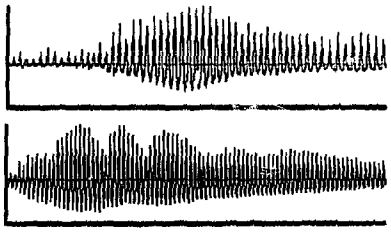
924-76 A New Non-Invasive Method for Detection and Assessment of Aortic Regurgitation During Routine Blood Pressure Recordings

Todd J. Brinton, Tsui-Lieh Hsu, Oi-Ling Kwan, Chun-Peng Liu, Mau Song Chang, Shiu-Shin Chio, Anthony N. DeMaria. *Veterans Hospital, Taipei, Taiwan, University of California, San Diego, CA*

Recently, we developed an oscillometric cuff technique (CUFF) to non-invasively derive arterial pressures and waveforms. Using this method we observed a unique pattern of pressure oscillations (PO) in a pt with severe aortic regurgitation (AR). To further define the potential mechanism of this phenomenon, and its value in the detection and assessment of AR, we performed clinical and modeling studies. CUFF was performed in 10 normal (N) and 15 pts in whom AR was documented and semi-quantitated by echo. In 10 N, and all 5 mild AR pts, a bell shaped distribution of PO was observed from supra-systolic to sub-diastolic cuff pressure (top figure). However, all 10 pts with grade III (severe) AR exhibited a phasic alteration of PO conforming to a resonance pattern (bottom figure). To test the hypothesis that this phenomenon represented a ventricular-vascular fluid mechanics interaction produced by AR, we utilized a simple amplitude modulation model (W1 = incident, W2 = reflection) and found that the pattern could be reproduced at specific amplitudes and frequencies.



Thus, CUFF recordings of arterial pressure exhibit a marked resonance pattern in pts with severe AR, likely due to ventricular-vascular fluid mechanics interaction. This phenomenon should be useful in detecting and assessing AR during routine blood pressure recordings.

925 Transplant Rejection

Monday, March 25, 1996, 3:00 p.m.–5:00 p.m.
Orange County Convention Center, Hall E
Presentation Hour: 4:00 p.m.–5:00 p.m.

925-1 Deterioration in Cardiac Function Is Associated With the Appearance of Specific HLA Antibodies After Transplantation

Stephen H. Leech, Paul J. Mather, Howard J. Eisen, Valluvan Jeevanandam. *Temple University Medical School, Philadelphia, PA*

The purpose of this study was to investigate the effect of HLA antibodies specific for mismatched donor HLA antigens appearing in the circulation after human orthotopic heart transplantation. Although there is increasing evidence of a deleterious effect of mismatched donor HLA antigens on the outcome of human cardiac allografts, the role of HLA antibodies remains controversial. Thus, their presence prior to cardiac transplantion has been associated not only with poor outcome by some workers but also of no clinical significance by others. Furthermore, their appearance after cardiac transplantion has also been the subject of conflicting reports. HLA antibodies were identified by a standard microlymphocytotoxicity technique using panels of frozen lymphocytes from normal donors who had been tissue typed. Of 78 patients transplanted over a 12-month period, 4 developed HLA antibodies specific for mismatched donor HLA antigens. The first patient developed antibodies to HLA-A23 and B44, which were associated with vascular rejection requiring retransplantation within 4 months. The other patients (3) developed antibodies specific for HLA-DQ7 and experienced variable numbers of episodes of cellular rejection with negative immunofluorescence on endomyocardial biopsy. Two of these 3 patients died (8 and 11 months post-transplant) after 3 and 6 rejection episodes respectively. The one surviving patient with DQ7-specific alloantibodies has had 7 rejection episodes and continues to have poor ventricular function (follow-up 13 months). We conclude that i) alloantibodies specific for mismatched donor HLA antigens may have a deleterious effect on the outcome of the human cardiac allograft and should be monitored closely post-transplant, and ii) that there may be special significance to the association with DQ7-specific alloantibodies.

925-2 Myocardial Apoptosis in a Heterotopic Murine Heart Transplant Model of Chronic Rejection/Graft Vasculopathy

Robert Shaddy, William White, Lynda Zhang, Michael Trautman, Sherrie Perkins, Elizabeth Hammond, Jane Shelby. *University of Utah and Primary Children's Medical Center, Salt Lake City, UT*

Apoptosis (programmed cell death) has been implicated in myocardial reperfusion injury and in experimental transplant rejection. One mechanism of apoptosis is through the interaction of the cell-surface fas receptor on target cells and the Fas ligand which is expressed on cytotoxic T cells. To determine whether apoptosis occurs in the myocardium of transplanted hearts, we examined a murine heterotopic heart transplant model of chronic rejection/graft vasculopathy (strain B10.A to B10.BR). Hearts harvested after 30 days showed an intimal index of the allografts (0.5 ± 0.1) (mean ± SE) that was 15 to 50 times more than syngeneic grafts (0.03 ± 0.01) and native (nontransplanted) hearts (0.01 ± 0.01) ($p < 0.001$). In situ end-labeling of partially degraded DNA with terminal deoxynucleotydil transferase showed an increase in apoptotic cells/20 hpf in allografts (2.0 ± 0.3) and syngeneic grafts (3.0 ± 0.4) compared to native hearts (0.0 ± 0) ($p < 0.001$, ANOVA). Both myocytes and nonmyocytes appeared to be undergoing apoptosis. RT-PCR detected equal myocardial RNA signal intensity of Fas in allografts, syngeneic grafts, and native hearts ($n = 4$). In contrast, allografts showed a strong signal for the Fas ligand mRNA, a signal not seen in syngeneic grafts or in the native hearts. We conclude that apoptosis is occurring in both murine cardiac allografts and syngeneic grafts and that Fas ligand is strongly expressed in murine allografts. Since both allografts and syngeneic grafts show in-situ evidence of apoptosis, but only allografts express Fas ligand, the mechanisms of apoptosis in this model may not be exclusively related to Fas/Fas ligand interactions.

925-3 Immunologic Characterization of Allograft-Infiltrating Cells in Human-Severe Combined Immunodeficiency Mouse Chimeras: Evidence for Human Effector Cell Mediation of Rejection

Jin Kang, Sheri E. Belland, Howard J. Eisen. *Temple University, Philadelphia, PA*

Novel immunosuppressive agents are initially tested in experimental animals, usually rodents. This approach often fails as there are substantial differences between human and rodent immune systems. We have developed a potential in vivo model of human cardiac transplant rejection by reconstituting severe combined immunodeficiency (SCID) mice with human peripheral blood lymphocytes (PBL's) and 28 days later implanting segments of human atrial tissue from patients undergoing CABG surgery subcutaneously (SQ) in the human-SCID chimeras. 7 days later lymphocytic infiltration and myocyte necrosis is seen in the cardiac allografts in these chimeras by hematoxylin and eosin staining, resembling human cardiac transplant rejection. The origin and type of cells infiltrating the grafts are unknown. To determine the phenotype and origin of these cells, we administered 5×10^8 PBL's intraperitoneally to 4 SCID mice and confirmed engrafting of human PBL's by flow cytometry: 3 control SCID mice were not reconstituted. Segments of human atrial tissue were implanted SQ in the human-SCID chimeras and control SCID mice. 7 days later, cardiac tissue was removed, and stained with human-specific anti-CD4, CD8, IL-2 receptor (R), CD3 and ICAM-1 antibodies. Infiltrating cells were seen in the reconstituted SCID mice and were primarily CD4+ and CD3+ with over 25% IL-2R+. No myocardial lymphocytic infiltration or myocyte necrosis was seen in the control SCID mice. Endothelial ICAM-1 expression was seen only in allografts in reconstituted SCID mice. We conclude that cells infiltrating cardiac allografts in human-SCID chimeras are human-derived, activated CD4+ similar to those seen in human cardiac allograft rejection and that they induce allograft endothelial activation.

925-4 Detection of Heart Transplant Rejection by Doppler Tissue Imaging

John A. Puleo, Mark W. Weston, Michael F. French, Guillermo Cintron, Mitchell G. Davis, Hector L. Fontanet. *Division of Cardiology, University of South Florida and Tampa General Hospital, Tampa, FL*

Heart transplant rejection (HTR) commonly occurs in heart transplant recipients and requires invasive endomyocardial biopsy (EB) for diagnosis. Thus far, non-invasive studies have had inadequate sensitivity to detect HTR. Pulsed wave Doppler tissue imaging (PWDTI) is a new non-invasive imaging modality capable of quantifying myocardial tissue velocities. Since HTR may cause disturbances in myocardial relaxation, we performed this study to determine whether moderate HTR results in reduced myocardial peak early relaxation velocities (PEV). *Methods:* 40 orthotopic heart transplant recipients underwent serial PWDTI at the time of routine surveillance EB. 10